The following is a complete listing of all claims in the application, with an indication of the status of each:

Listing of claims:

We claim:

1. (Original) A computer-assisted method for creating and displaying a model of a molecule in which the residues of said molecule that are affected by binding of a ligand to said molecule are highlighted using a programmed computer including a processor , an input device, and an output device, comprising,

inputting into said programmed computer, through the input device, data including an identity and three-dimensional coordinates of said molecule,

generating, using the processor, a conformational ensemble for said molecule, wherein said conformational ensemble is comprised of a number of conformational states of said molecule sufficient to achieve convergence to a stable ensemble average,

determining, using the processor, a predicted Gibbs energy for each of said conformational states,

identifying, using the processor, binding competent conformational states,

modifying said predicted Gibbs energy for said binding competent conformational states to form a modified Gibbs energy using an equation

$$\Delta Gi = \Delta Gi^0 - RT \ln \frac{(1 + Ka,i\,[X])}{(1 + Ka,_0\,[X])}$$

wherein ΔGi is said modified Gibbs energy, ΔGi^0 is said predicted Gibbs energy, R is a gas constant, T is an absolute temperature, $Ka,_0$ is a binding constant to a reference state, $Ka,_i$ is a binding constant to a given binding competent conformational state, and [X] is a concentration of said ligand,

forming, using said processor, a first and second set of Gibbs energy values, wherein said first set of Gibbs energy values represents Gibbs energy values in the presence of said ligand and said second set of Gibbs energy values represents Gibbs energy values in the absence of said ligand,

computing, using the processor, a first set of probabilities from said first set of Gibbs energy values and a second set second of probabilities from said second set of Gibbs energy values, wherein said first set of probabilities represents probability values in the presence of said ligand and said second set of probabilities represents probability values in the absence of said ligand,

calculating, using the processor, a first set of residue stability constants in the presence of ligand from said first set of probabilities and a second set of residue stability constants in the absence of ligand from said second set of probabilities,

comparing, using the processor, said first and second sets of residue stability constants,

selecting affected residues of said molecule, wherein said affected residues exhibit a difference in stability constant in said first and said second set of stability constants,

creating, using the processor, a model of said molecule wherein said affected residues are highlighted, and

displaying, using the output device, said model of said molecule wherein said affected residues are highlighted.

Claim 2 (Original). The method of claim 1 wherein said step of identifying binding competent conformational states comprises the steps of

ascertaining a contribution of each residue of said conformational states in said ensemble to the Gibbs energy of binding for said ligand,

defining binding determinant residues, wherein said binding determinant residues contribute in excess of about 100 cal/mole to the Gibbs energy of binding, and

establishing as binding competent conformational states those conformational states in which said binding determinant residues are in a native conformation.

Claim 3 (Original). The method of claim 1 wherein said molecule is a protein.

Claim 4 (Original). A computer program product comprising a computer-readable medium having stored thereon a computer program including instructions for causing a computer to:

receive data including an identity and three-dimensional coordinates of a molecule,

generate a conformational ensemble for said molecule, wherein said conformational ensemble is comprised of a plurality of conformational states of said molecule,

determine a predicted Gibbs energy for each of said plurality of states in said conformational ensemble,

identify binding competent conformational states,

modify said predicted Gibbs energy for said binding competent conformational states to form a modified Gibbs energy using an equation

$$\Delta Gi = \Delta Gi^0 - RT \ln \frac{(1 + Ka,i\,[X])}{(1 + Ka_{,0}\,[X])}$$

wherein ΔGi is said modified Gibbs energy, ΔGi^0 is said predicted Gibbs energy, R is a gas constant, T is an absolute temperature, $Ka_{,0}$ is a binding constant to a reference state, $Ka_{,i}$ is a binding constant to a given binding competent conformational state, and [X] is a concentration of said ligand,

compute a first set of probabilities from said first set of Gibbs energy values and a second set second of probabilities from said second set of Gibbs energy values, wherein said first set of probabilities represents probability values in the presence of said ligand and said second set of probabilities represents probability values in the absence of said ligand,

calculate a first set of residue stability constants in the presence of ligand from said first set of probabilities and a second set of residue stability constants in the absence of ligand from said second set of probabilities,

compare said first and second sets of residue stability constants,

select affected residues of said molecule, wherein said affected residues exhibit a difference in stability constant in said first and said second set of stability constants,

create a model of said molecule wherein said affected residues are highlighted., and

display said model of said molecule.